RECRUITMENT OF RESEARCH SUBJECTS

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Abstract: *This article focuses on the ethical considerations that must be taken into account when recruiting subjects for clinical research. These ethical considerations are divided into three categories: selection, recruitment, and enrollment. The issues of providing the potential subject with sufficient opportunity to consider participation and minimizing coercion and undue influence during the informed consent process are highlighted.*

To put the issue of recruitment of research subjects into context, we know that clinical research is the search for knowledge useful to understanding and improving health. Clinical research requires the study of human subjects in order to be able to understand human health. Recruitment of subjects for clinical research is critical. In order to be able to successfully complete a study, recruitment must be timely, and the right number and type of subjects must be enrolled.

There is limited literature on the ethical considerations that must be taken into account when recruiting subjects for clinical research. Since the purpose of clinical research is to generate knowledge and not necessarily to directly benefit people, protecting subjects from possible exploitation or harm in the conduct of research is always a concern. This is the basis for all ethical requirements and regulations. Careful attention to the selection, recruitment, and enrollment of subjects in research, both individually and in groups, is fundamental to protecting subjects from exploitation and harm.

Selection of Research Subjects

After the research question is determined, the first consideration is who the desired subjects are (Table 1) in order to be able to answer that question. Researchers must consider how many subjects are needed to achieve adequate power and statistical capability. Once those matters are determined, other considerations come into play. Ethically, people should not be excluded from research participation without a good reason. Recent NIH guidelines require efforts to include women, ethnic minorities, and children in research.

The Common Rule (45 CFR 46.11(a)(3)) mandates that the IRB consider whether selection of subjects is equitable. The rule states: "In making this assessment the IRB should take into account the purposes of the research and the setting in which it will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations." This statement provides a sense that the scientific question drives selection of research subjects but directs researchers and IRBs to think about equitability in selection and providing additional protection to people who are vulnerable. The issue of equitable subject selection was first articulated in writing in the Belmont Report, which calls for ". . . fair procedures and outcomes in the selection of research subjects." Fair distribution of the benefits and burdens of research should be examined carefully for every research protocol. A recent shift in attitude about participation in research is of note. Federal regulations and available codes of research ethics reflect a very strong emphasis on protection of research subjects from the burdens of research, but during the 1990s, a pendulum swing occurred in which potential subjects began to demand access to the benefits of research. AIDS and breast cancer activists and others are advocate access to the benefits of participation in clinical research.

NIH guidelines that require investigators to include women, ethnic minorities, and children in research are based on the notion that participation in a study often benefits groups in society as well as the indi-

vidual subject. In order to use information from clinical trials to treat women, ethnic minorities, or children, who might be biologically different in terms of their response to treatment, these groups must be included in research studies.

In addition to thinking about benefits, we must consider whether some individuals are more susceptible to risk than others, and whether that potential for risk is so great that they should be justifiably excluded from the study.

Consideration of who will receive the benefits of research goes beyond the inclusion of women, ethnic minorities, and children in the United States, and is a central issue in debates about international research.

In summary, subject selection is based on scientific determination of who the appropriate subjects are to answer the question, consideration of the risks and benefits for those individuals and groups, and then a delineation of eligibility and exclusion criteria. All of that must be done before recruitment is begun. The next task is to find, recruit, and enroll the subjects.

Recruitment of Research Subjects
Recruiting subjects includes both the challenge of getting information to the people whom you want to recruit and getting them interested in the study that you are conducting. Recruitment is usually conducted through advertisements, targeting certain groups of potential subjects, and sometimes offering incentives. Advertisements are sometimes placed in general newspapers, on the Internet, in specialty journals , or on flyers in medical office or clinic waiting rooms. Methods of targeting certain groups might include requesting permission to recruit subjects from a specific clinical practice or asking someone from that group to refer subjects to you, or accessing people through patient databases or disease advocacy groups.

Researchers also often offer incentives to provide people with a reason to participate in a study. There is a fine line, however, between arousing interest in the study and avoiding exploitation and coercion. Incentives in the form of money, equipment such as computers, vacations, authorship, and so forth are sometimes offered to physicians and others who refer patients to clinical trials, but this practice is very controversial. In June 2000, the Inspector General published a report on recruiting subjects that made a number of recommendations for improving recruitment practices, including advertising, targeting, and offering incentives.

Enrollment of Research Subjects
Enrollment of study subjects begins after developing eligibility criteria and advertising or targeting subjects (Table 2). At this point, the process begins to shift from what we usually consider recruitment to what we usually consider informed consent, but it may be thought of more as a continuum. Informed consent begins when you advertise for subjects. The informed consent process includes:

- providing information to potential subjects,
- assessing a potential subject's ability to understand and his/her understanding of the particular information about a study,
- allowing the potential subject to make a free choice about participation, and
- documenting that choice in the form of a signature on an informed consent document.

The informed consent process is part of enrollment of research subjects.

Regulatory and Ethical Considerations in Selection, Recruitment, and Enrollment of Research Subjects
Federal regulations and ethical considerations guide the process of selection, recruitment, and enrollment of study subjects. The Common Rule states that investigators are required to obtain a legally effective informed consent from the subject or the legally authorized representative in every case unless there is a waiver approved by an IRB. Federal regulations require that researchers seek consent "only under circumstances that provide the prospective subject or representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion of undue influence."

Determining what "a sufficient opportunity to consider" is and "minimizing coercion and undue influence" are not straightforward issues. There are many ways to think about minimizing the possibility of coercion and undue influence during the informed consent process. Information provided must be accurate and adequate. For example, the Inspector General report expressed concern about whether some advertising for clinical research is misleading, and causing people to expect therapy rather than a clinical research study. Information provided to potential subjects should lead to a clear understanding about the research.

In order to allow potential subjects to make a free decision about participating in research, pressure from physicians or other people, or circumstances, must be minimized. Studies have shown that recruiting subjects through their personal physicians can be problematic. For example, the Advisory Commission on Human Radiation Experiments survey of 1,000 patients who participated in research studies reported that many respondents said that they participated in research because their doctor told them to. A few institutions have rules that prevent a physician who is taking care of a patient from enrolling that patient in his/her research. This is consistent with a statement in the Declaration of Helsinki advising caution in obtaining consent from someone in a 'dependent relationship' with their physician.

The circumstances under which people make decisions should be as free of influence as possible, recognizing that the influence of circumstances is hard to separate out. We are all influenced by a myriad of different things, including our health and social conditions. Imagine, for example, a person who has a disease for which he/she has already exhausted standard available therapies and is now being offered the option of clinical research, or a person who has no health insurance or no way to access treatment for his/her disease who reads about a free investigational treatment for that disease. How free is the decision to participate in research when the person's options are so limited or non-existent?

Incentives and Undue Inducement

There is not a clear line between motivations to participate in research and incentives. In fact, one definition of incentives is "motivational reasons." The limited research about what motivates people to participate in clinical research suggests that people participate primarily for the hope of therapeutic benefit. Other reasons include trust in their physicians, to help others with the disease and future generations, for medical care they cannot get elsewhere, for money, and for academic rewards (for student subjects). Incentives, which include access to treatment, free care, money, quid pro quo, and, promotions/grades/references (for student subjects) overlap with motivations in many ways.

Since the researcher must minimize coercion and undue influence according to the Common Rule, the problem becomes finding a line on the continuum of incentives, from motivational to undue influence, and determining what undue influence is and how to recognize and avoid or minimize it. Undue influence is often described as: "an offer one cannot refuse." That makes sense at some level but it is very hard to recognize. Others describe undue influence as "a controlling and irresistible influence." The IRB Guidebook of the Office for Human Research Protections provides helpful advice about undue influence, stating that it is problematic for two main reasons:

1. Sometimes offers are so attractive that they impair people's judgment, and people will accept risks and do things that they would not or should not otherwise do because the offer is the only thing that they can see.
2. An overly attractive offer might cause potential subjects to misrepresent themselves because they want to be eligible for a study. This is a problem both for the safety and well-being of the subject as well as the validity of the data.

TABLE 1
Selection and Recruitment of Research Subjects

- Determine which subjects are needed for scientific reasons
- Consider the risks and benefits for individuals and groups
- Establish eligibility and exclusion criteria
- Find, inform, recruit, and enroll sought-after subjects

TABLE 2
Enrollment of Research Subjects

- Invite subjects to participate in a study
- Provide the information needed for the potential subject to evaluate the risks, benefits, and alternatives and make a considered decision about participation (ie, informed consent)
- Screen and sign on subjects, and begin study procedures